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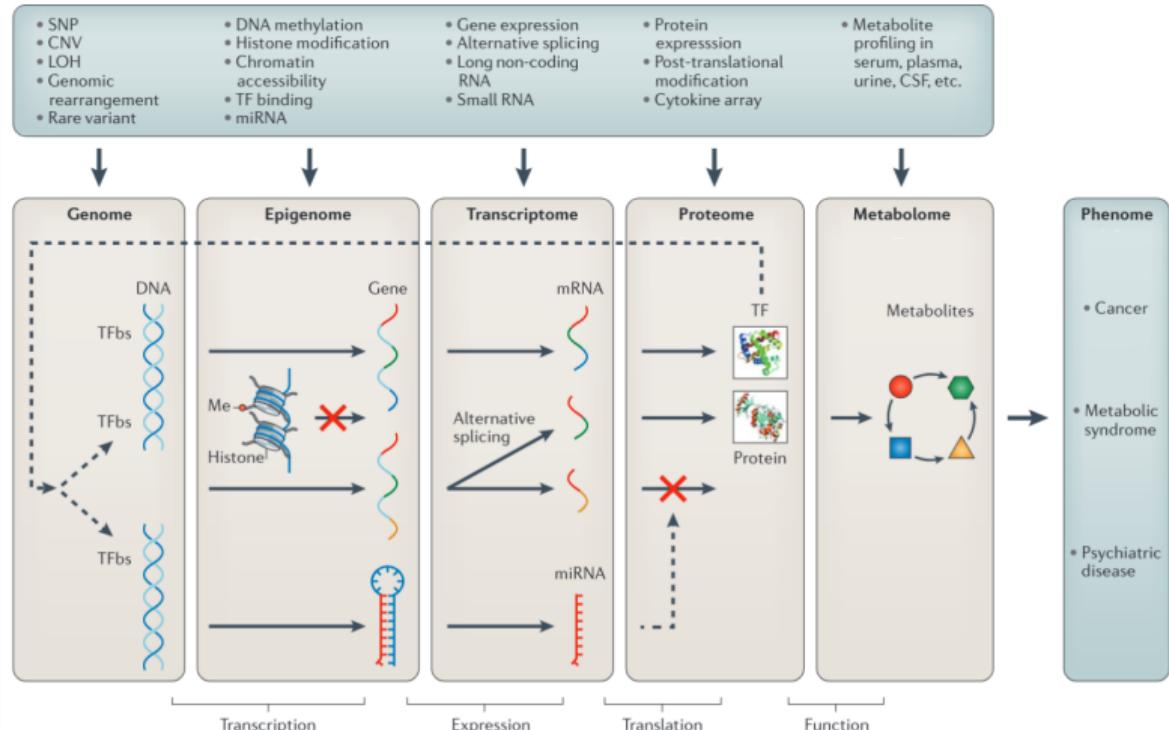
Accessible and Reproducible Analyses with the CoLoMoTo notebook

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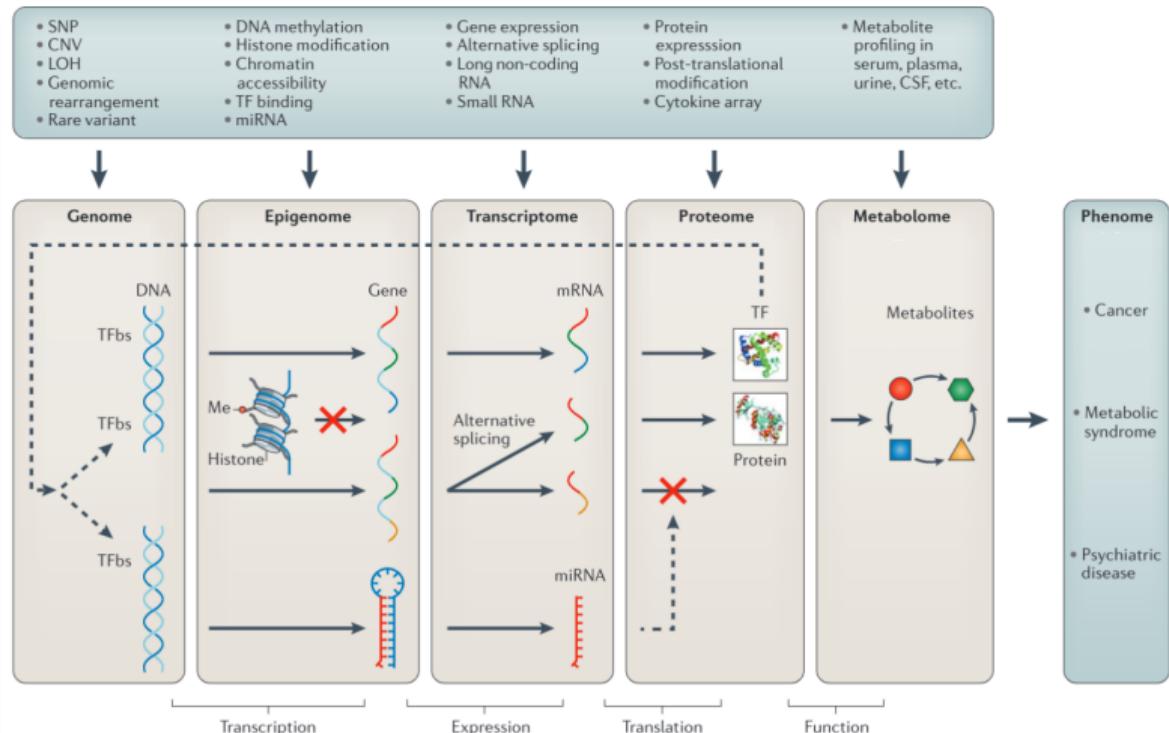
WTAC 2022 - Computational Systems Biology

Cell is tightly regulated at several levels



(Ritchie et al., *Nat. Rev. Gen.* 2015)

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We need to make sense of all heterogeneous information!

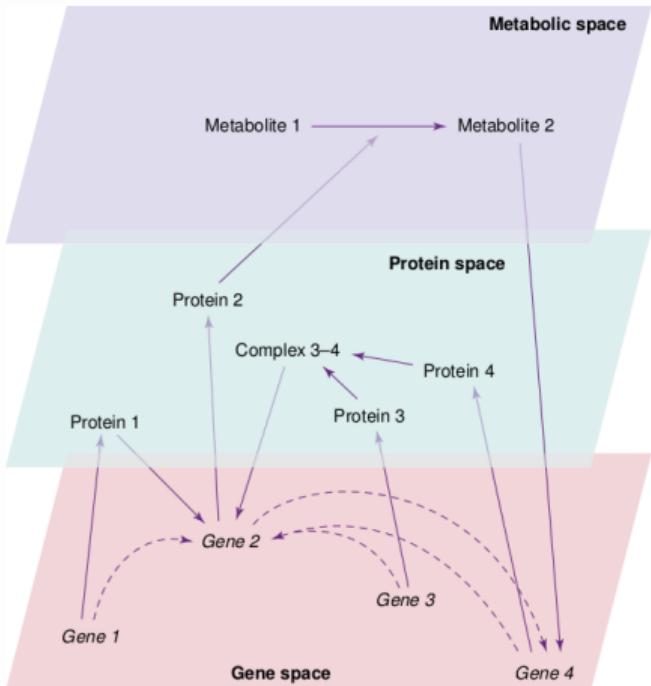
Gene regulatory networks

- consist of genes, gene products (RNA, proteins), and the regulatory effect of the latter on the expression of other genes

(Bolouri *et al.*, *Computational Modeling of Gene Regulatory Networks* 2008)

- cannot be reduced to direct interactions (transcriptional regulation), but also include indirect interactions (mediated by metabolism)

(Brazhnik *et al.*, *Trends Biotechnol* 2002)



Different levels

Structural → Dynamical view

Network components need to be quantified:

- Values change over time (created / consumed)

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⇒ We need something to describe the system' evolution!

(Kitano, *Science* 2002)

Structural → Dynamical view

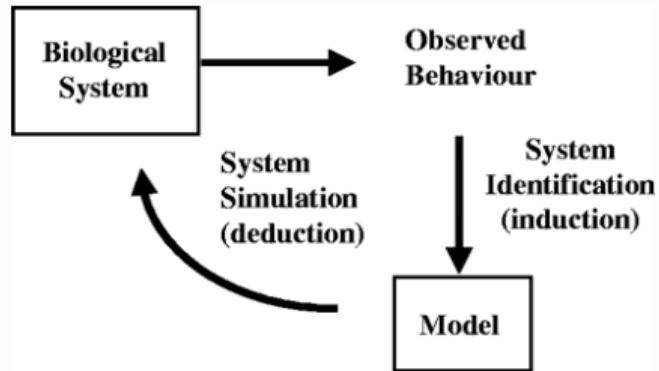
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Rely on models to analyse networks

- Understand of the way in which particular molecular mechanisms control a cellular process
- Predict novel phenomena that can be confronted with experimental data



(King, Garrett and Coghill, *Bioinformatics* 2005)

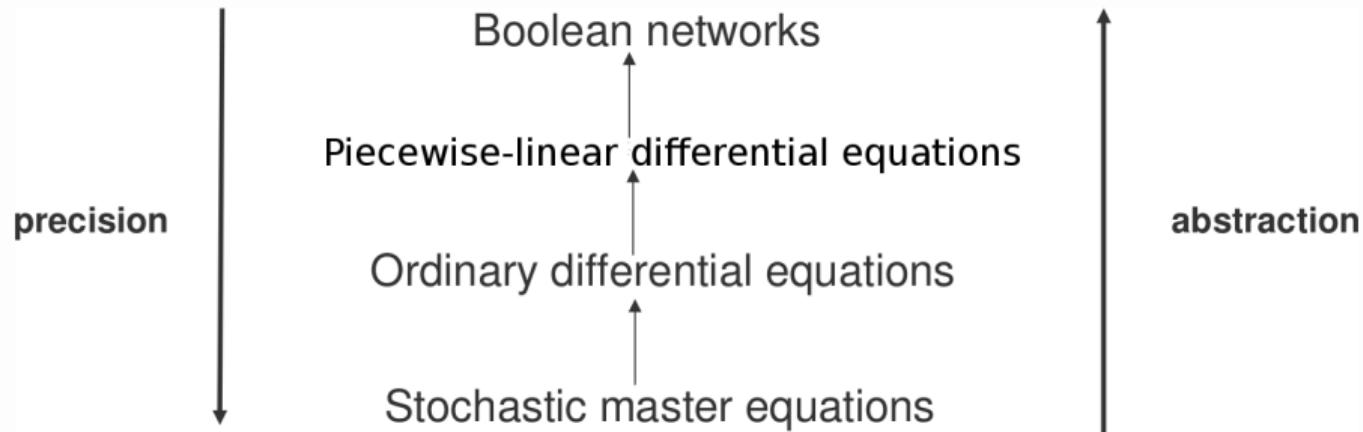
Formalisms

A variety of physical and mathematical approaches have been used:

- Non-linear
- Piecewise-linear
- Logical (Boolean networks)
- Petri nets
- Statistical-mechanical
- Stochastic

Hierarchy of modeling formalisms

Describe the system at different levels of detail (e.g. continuous vs qualitative)



(de Jong, *J. Comput. Biol.* 2002) (Hasty et al., *Nat. Rev. Genet.* 2001)

(Smolen et al., *Bull. Mat. Biol.* 2000) (Szallasi et al., *Systems Modeling in Cellular Biology* 2006)

Well established qualitative formalisms for modeling gene regulatory networks:

- Piecewise-linear differential equations (PLDEs)

(Glass and Kauffman, *J. Theor. Biol.* 1973)

- **Logical formalism**

(Boolean networks)

(Thomas et al., *Bull. Math. Biol.* 1995)

- Petri nets, ...

- Lack of quantitative data
(ON/OFF mechanisms, thresholds)
- Discrete time

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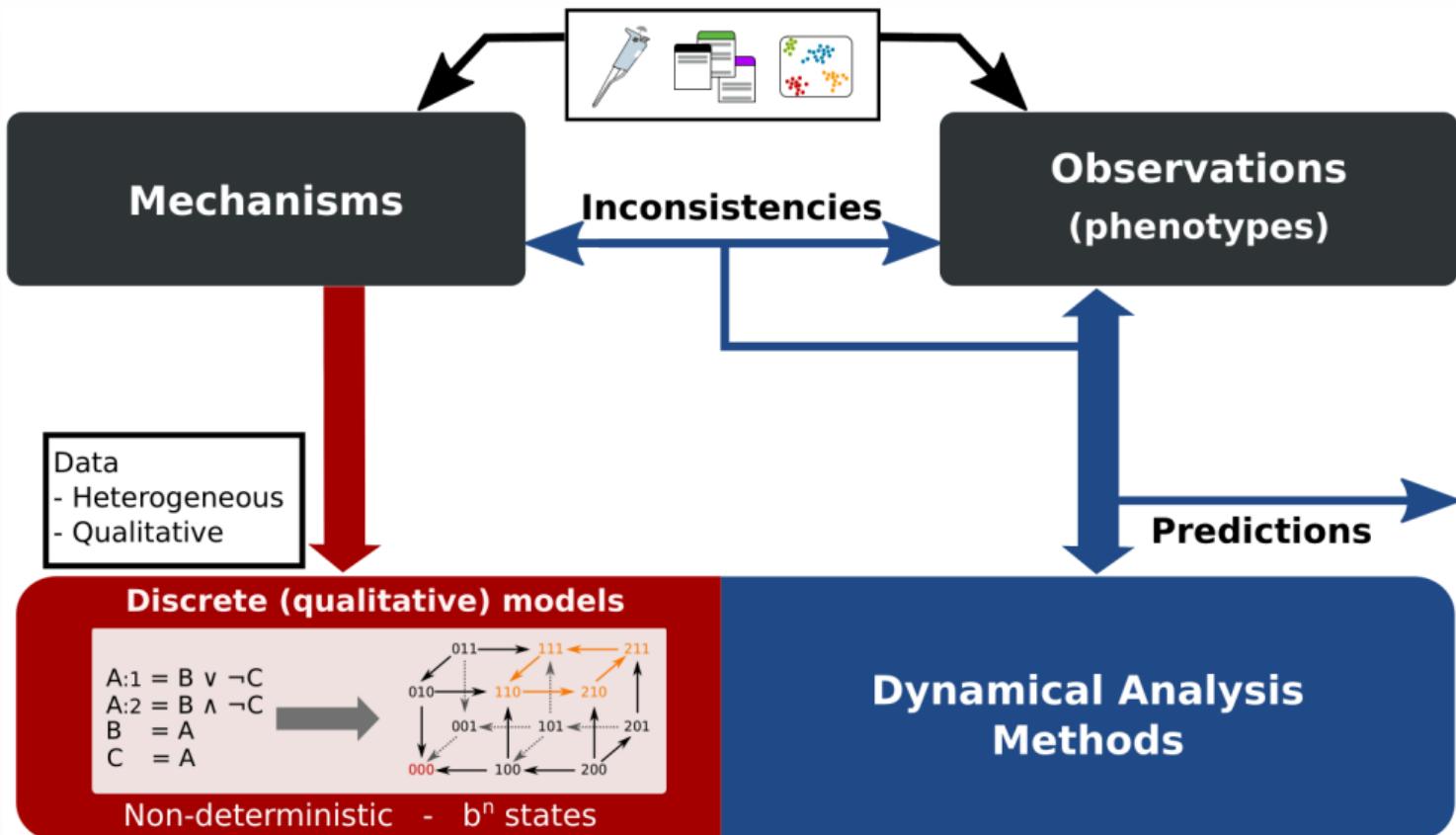
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Implicit assumptions

- Ignore intermediate gene products (mRNA)
- Ignore gene expression machinery (RNA polymerase, ribosome)
- Simplification of complex interactions of regulators with DNA to single response function

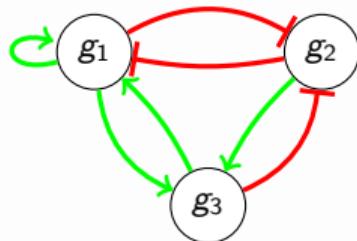


	Wet lab	Dry lab
Material	Biological material: - Cell type - Genetic background	Dataset - Source - Format
Tools	Chemicals & Machines - Provider, batch number	Software - Exact version
Protocol	List of operations	Commands, parameters

Minor details may play a crucial role

Regulatory graph

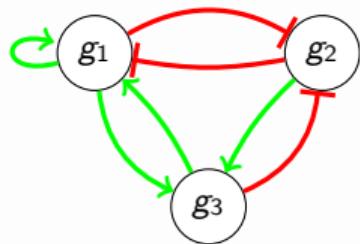
- Is a tuple (G, E) where G denotes a set of nodes/vertices (eg. gene expression) and E a set of edges
- An edge $(i, j) \in E$ indicates that i regulates the expression of j
- Edges can have sign information about interactions:
 - . $(i, j, +)$ for “ i activates j ”
 - . $(i, j, -)$ for “ i inhibits j ”



Boolean model (regulatory graph + logical rules) $\mathcal{M} = (G, K)$

(Thomas and d'Ari, *Biological Feedback* 1989)

- $G = \{g_i\}_{i=1,\dots,n}$ is a set of n regulatory components
- $\prod_{g_i \in G} \{0, 1\}$ defines the state space S
- K is the set of regulatory functions $K_{g_i} \in K : S \rightarrow \{0, 1\}$

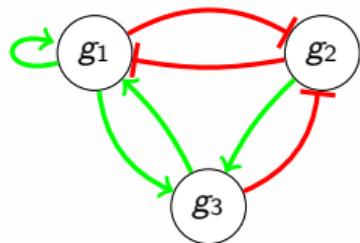


$$\begin{aligned}K_{g_1}(x) &= x_1 \vee \neg x_2 \vee x_3 \\K_{g_2}(x) &= \neg x_1 \vee \neg x_3 \\K_{g_3}(x) &= x_1 \wedge x_2\end{aligned}$$

- Gene expression has two (or more) levels: **0** (Inactive) and **1** (Active)
- K_{g_i} is a combination of basic Boolean operators: \neg , \wedge and \vee

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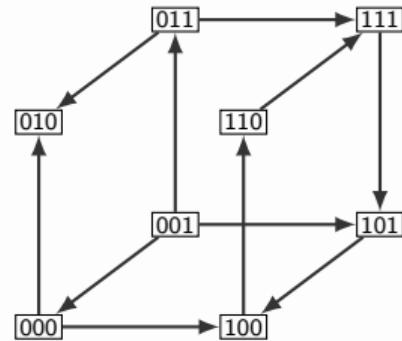
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No quantitative parameters but requires a precise description of competing effects

State transition graph (STG)

- Represents the dynamics of the Boolean model
- Nodes are states in \mathcal{S}
- Arcs $(i, j) \in \mathcal{S}^2$ denote transitions between states

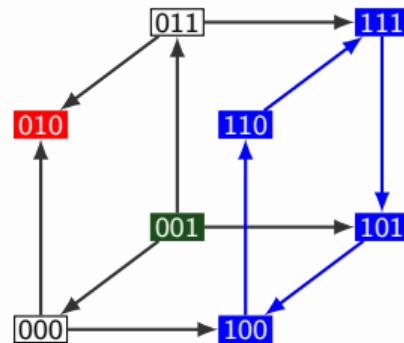
Successor state: $\forall_{g_i \in G}, g_i^{t+1} = K_{g_i}(g_1^t, \dots, g_n^t)$



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Attractors

Correspond to (biologically relevant) asymptotic behaviours

- **Stable state:** all gene levels are maintained
e.g., differentiated states, death, ...
- **Complex attractor:** long-lasting oscillatory behaviour
e.g., cell cycle, ...

Interesting properties

- What are the attractors of the system? (stable states, complex attractors)
Is there multistability?
- Are these attractors reachable from initial conditions?
- Are these attractors maintained under input variations?
- What is the likelihood of reaching an attractor from a given portion of the state space?
- ...

Combinatorial explosion of number of states

# Components	# States	
	Boolean	3-valued
3	8	27
10	1 024	59 049
20	1 048 576	3 486 784 401
30	1 073 741 824	205 891 132 094 649
40	1 099 511 627 776	12 157 665 459 056 928 801

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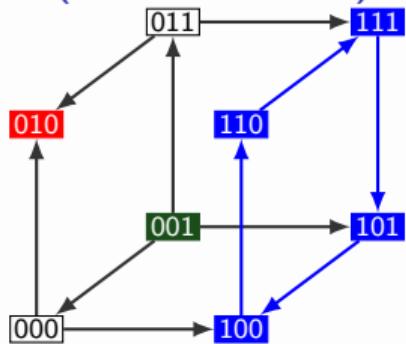
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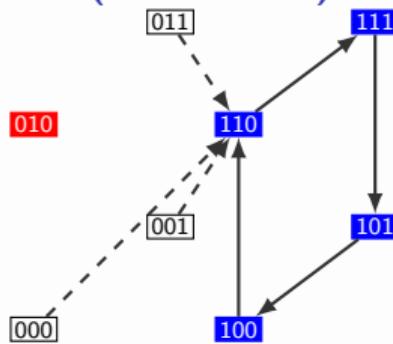
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- As the model size increases \Rightarrow manually intractable
- State transitions graphs are not practical for most current models
- **Logical models enable efficient analytical methods**

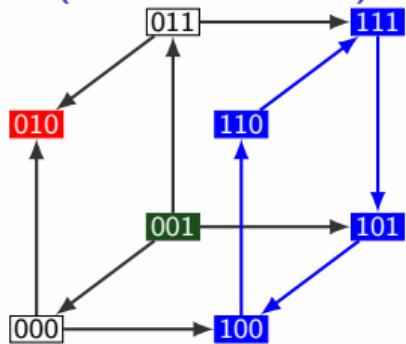
Asynchronous updating (non-deterministic)



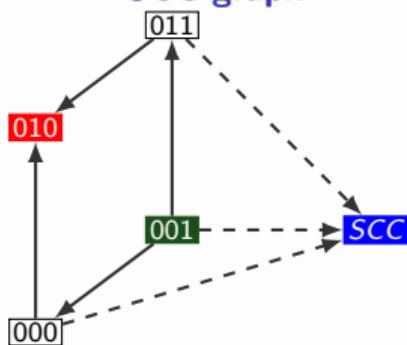
Synchronous updating (deterministic)



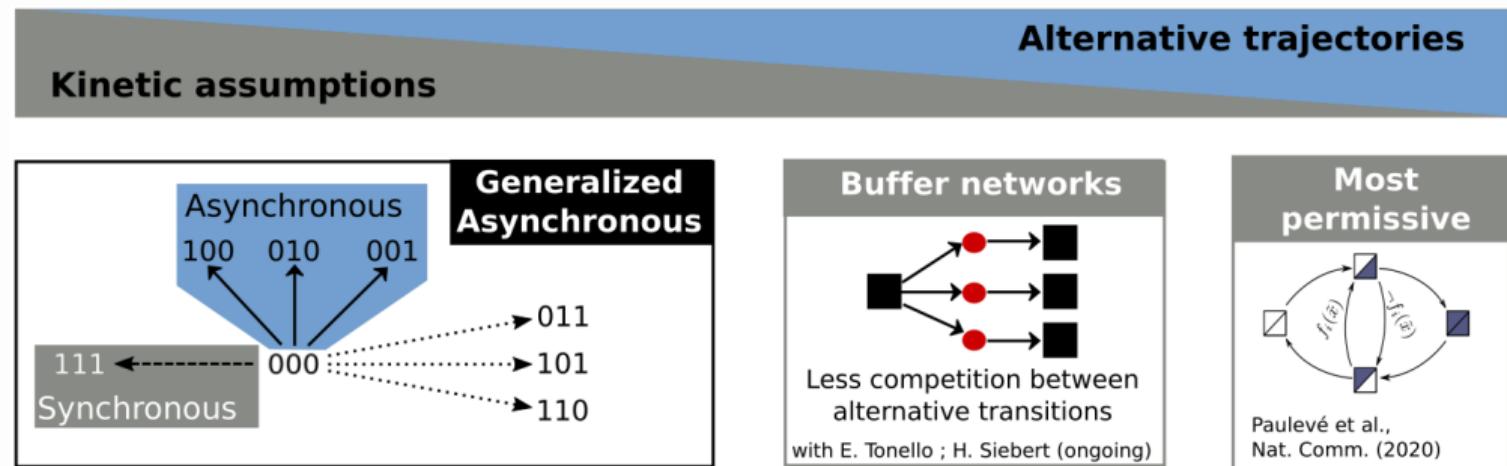
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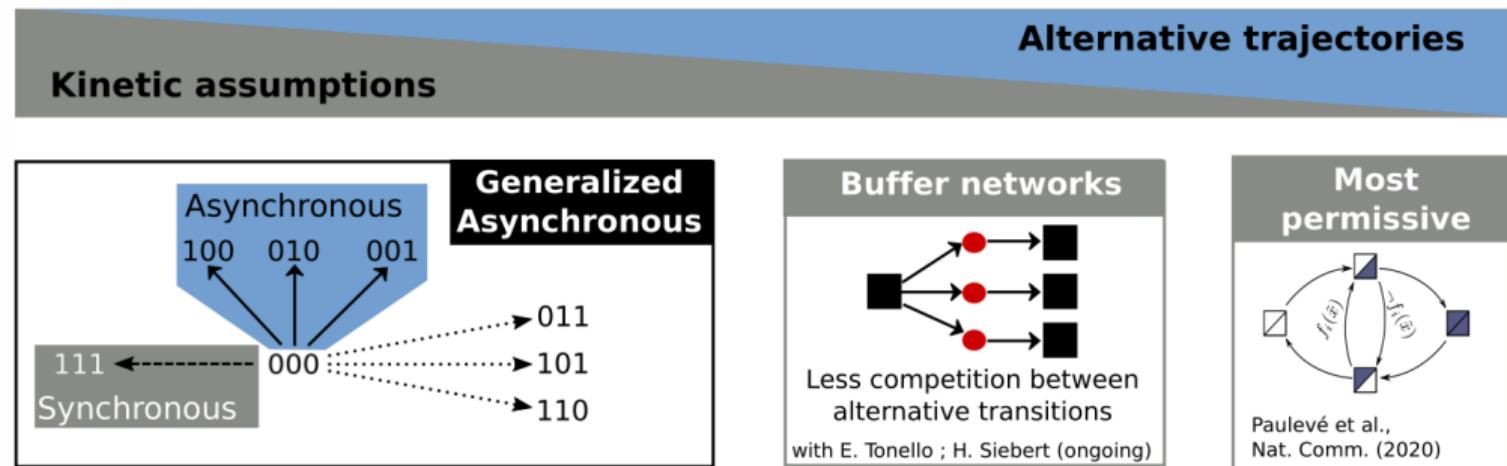
SCC graph



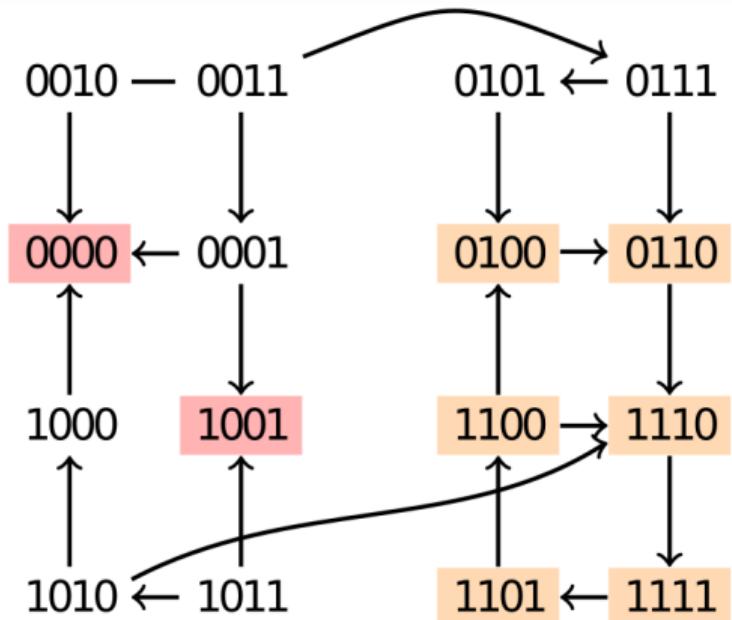
Explosion of number of transitions

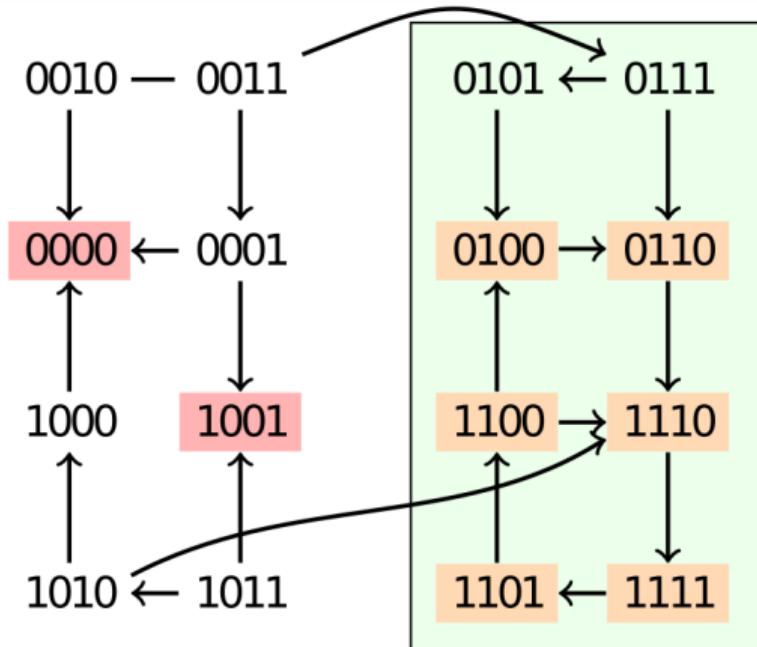


Explosion of number of transitions



In absence of kinetic knowledge,
many alternative trajectories are possible





Trap spaces
(stable patterns/hypercubes)

hypercube h :
 $\forall x \in h, f(x) \in h$

Constraint solving Zanudo et al., 2013
 Klarner et al., 2014

Stable states (fixed points)

state x : $f(x) = x$

Constraint solving

Naldi et al., 2007

Complex attractors

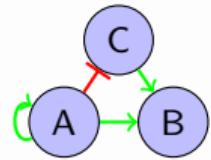
states C : $\forall x \in C, F(x) = C$

Symbolic exploration

Garg et al., 2008

Methods: stable states identification

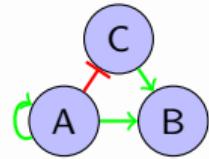
(without explicit state exploration)



(Naldi et al., CMSB 2007)

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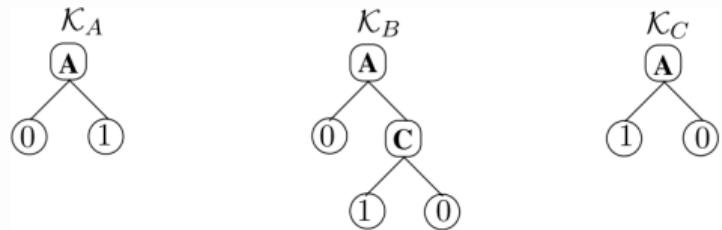
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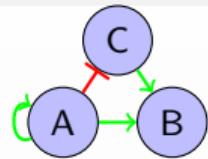
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Logical functions as OMDDs (Ordered Multivalued Decision Diagrams):



Methods: stable states identification

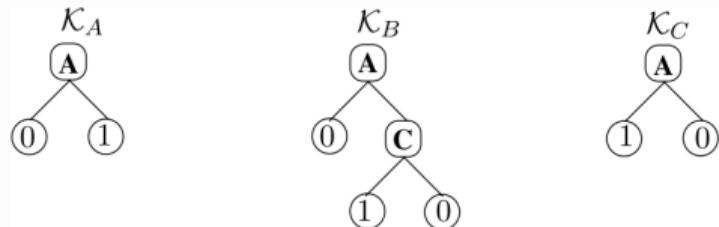
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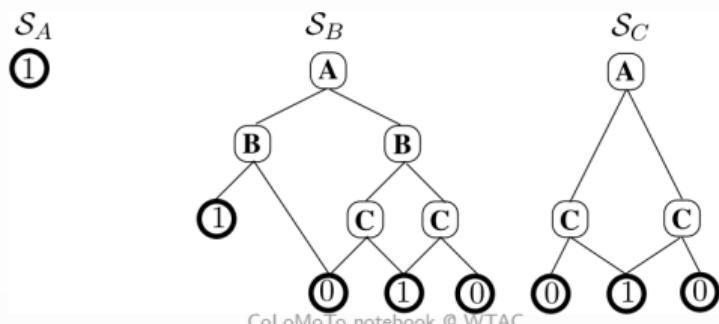
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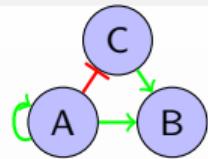


Stability conditions as OMDDs:



Methods: stable states identification

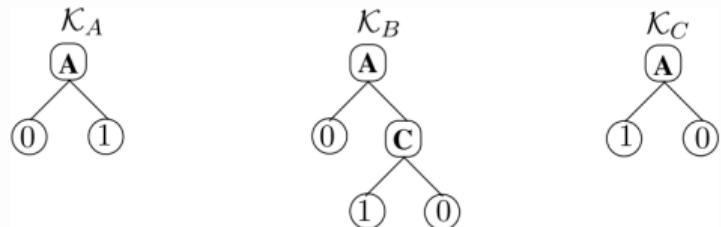
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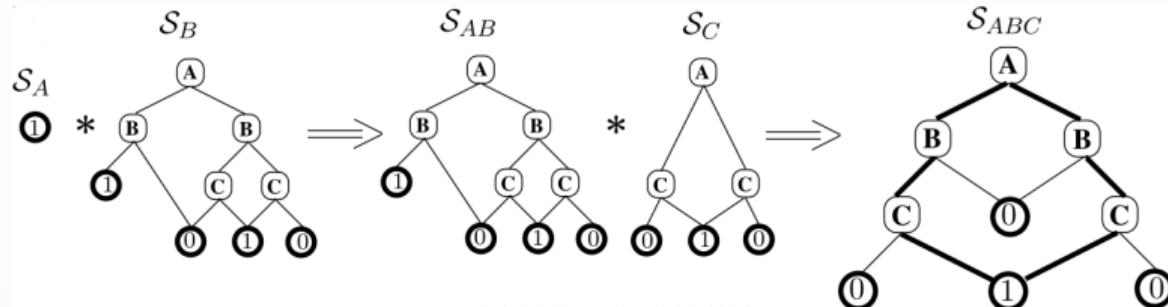
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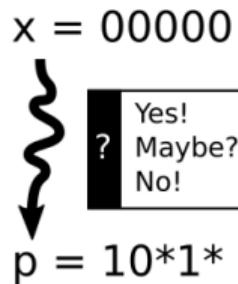
Identification of existing reachability

Explicitly generating the whole STG or ...

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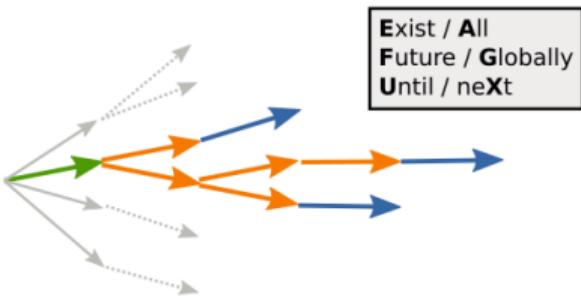
Explicitly generating the whole STG or ...

Pint: efficient, based on the topology



Pauleve et al., 2012

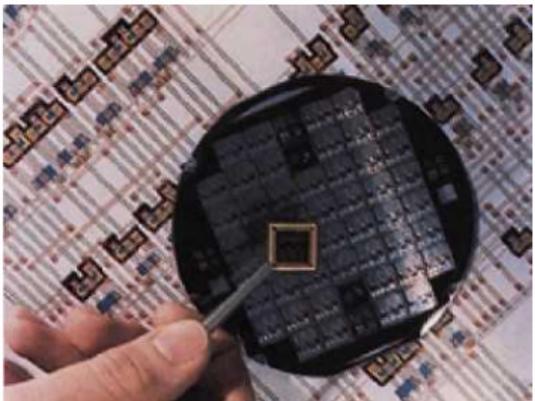
NuSMV: model checking



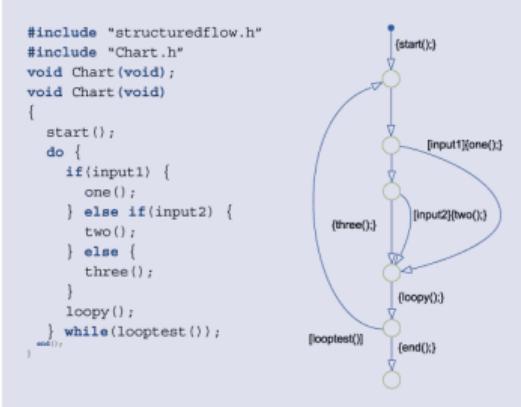
Monteiro et al., 2014

Model checking

Developed since the 70s, for hardware and software verification

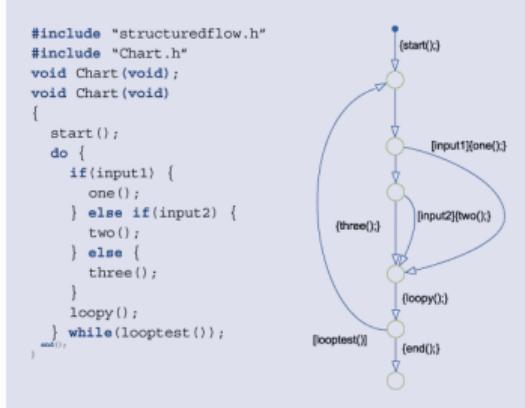
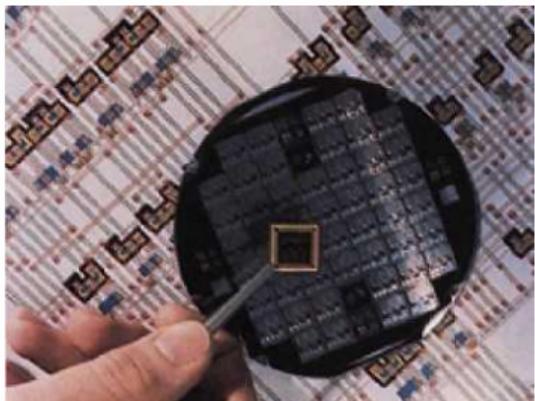


```
#include "structuredflow.h"
#include "Chart.h"
void Chart(void);
void Chart(void)
{
    start();
    do {
        if(input1) {
            one();
        } else if(input2) {
            two();
        } else {
            three();
        }
        loopy();
    } while(looptest());
    end();
}
```



Model checking

Developed since the 70s, for hardware and software verification



Application to Systems Biology

- MAPK signalling pathway
- ERK intracellular signalling pathway
- Carbon starvation response in *E. coli*
- FLR1 gene mancozeb response in *S. cerevisiae*
- T-helper cell differentiation

(Chabrier-Rivier et al., *Theor. Comput. Sci.* 2004)

(Calder et al., *CMSB* 2005)

(Batt et al., *Bioinform.* 2005)

(Monteiro et al., *IET Syst Biol* 2011)

(Abou-Jaoudé et al., *Frontiers in Bioeng. Biotech.* 2015)

Temporal logic

Formalism for describing sequences of transitions between states in a reactive system

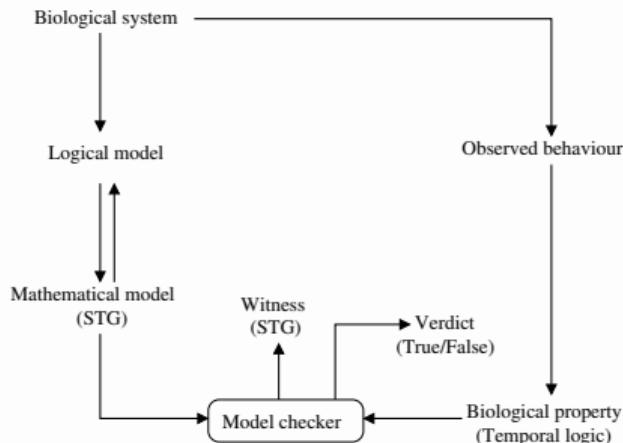
- CTL - Computation Tree Logic (branching-time)
- LTL - Linear Temporal Logic (linear-time)
- CTRL - Computation Tree Regular Logic
- ...

(Clarke et al., ACM T.P.L.S. 1986)

(Clarke et al., Model Checking 2000)

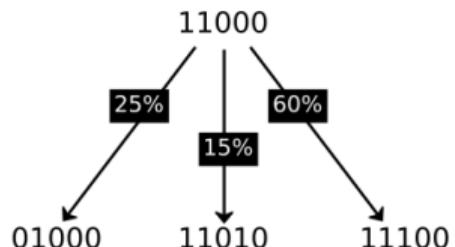
(Mateescu et al., Theor. Comput. Sci. 2011)

Outline of approach



Quantification of reachability

Probabilities of transition
(firing rates)

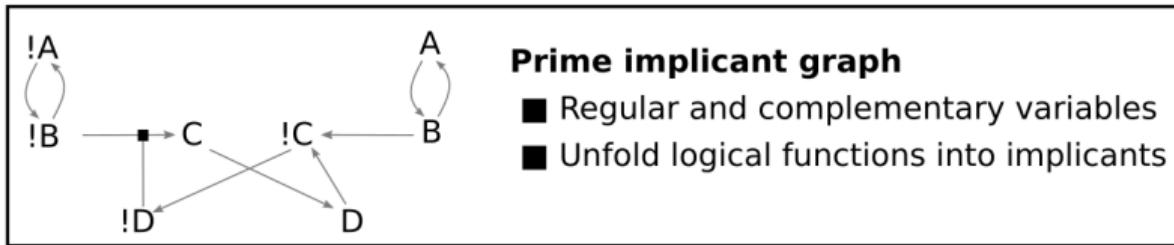
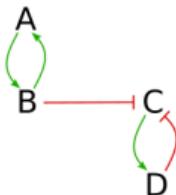


Estimated distribution
of state's probabilities



Stochastic simulations

- **Avatar** ([Mendes et al., Frontiers in Physiology 2018](#))
- **MaBoSS** ([Stoll et al., BMC Syst Biol 2012](#))



Manipulate satisfiable variables

- The initial set is given by the initial state
- An implicant is satisfied if all required variables are satisfied
- A variable is satisfied if at least an implicant is satisfied

Well suited for the most permissive semantics

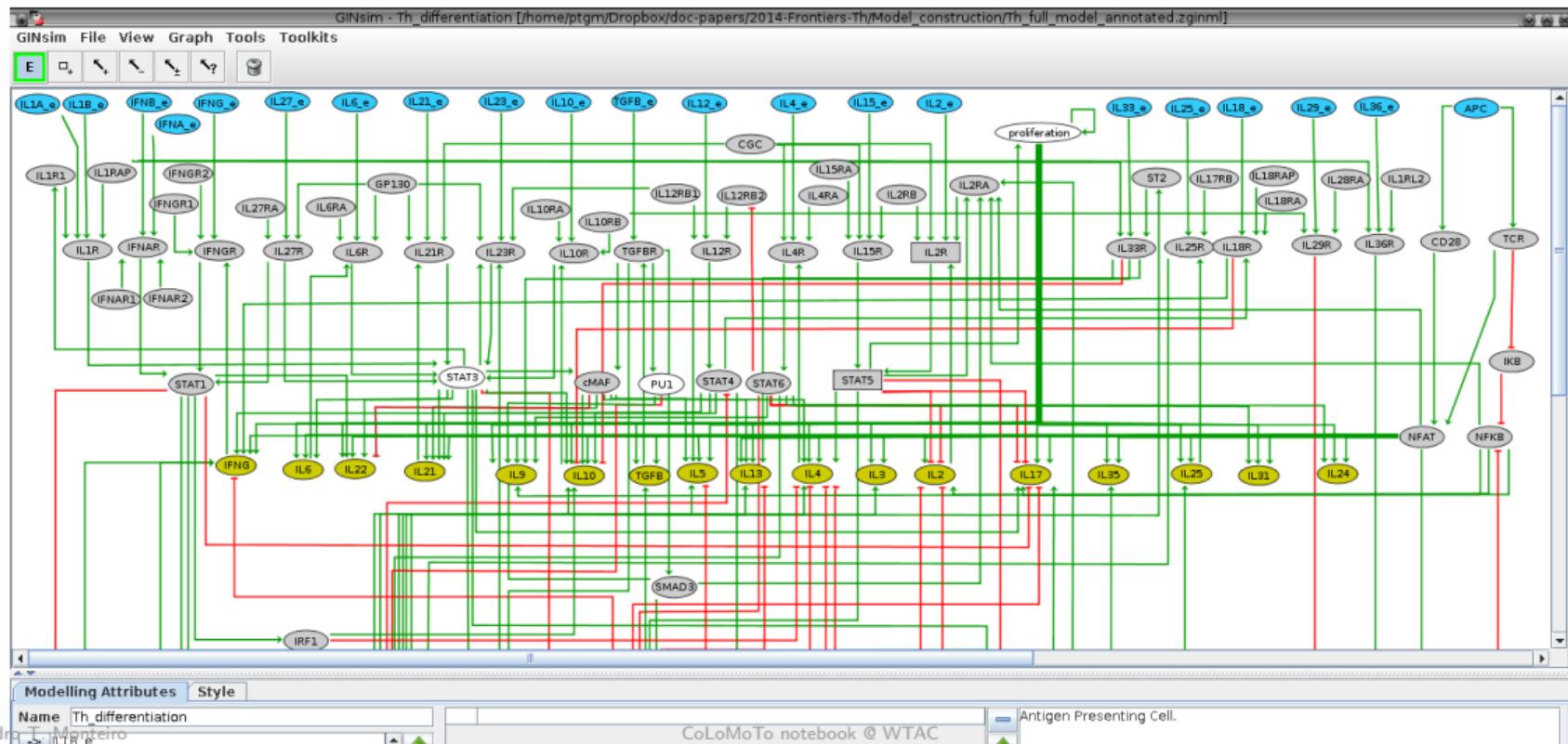
Over-approximation of the asynchronous updating

- Provide an answer in some cases
- May require a more precise (slow) refinement

Gene Interaction Network simulation - GINsim

Gene Interaction Network simulation is a computer tool for the modeling and simulation of genetic regulatory networks implementing the **logical formalism** <http://ginsim.org>

<http://ginsim.org>



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<http://ginsim.org>

Analysis methods

Static Analysis:

- Stable state search
(Naldi *et al.*, CMSB 2007)
- Circuit analysis
(Thieffry, *Brief. Bioinform.* 2007)
- Model reduction
(Naldi *et al.*, *Theor. Comput. Sci.* 2011)

Dynamics:

- STG construction
- HTG construction
(Bérenguier *et al.*, *Chaos* 2013)
- Priority classes
(Fauré *et al.*, *Bioinform.* 2006)
- Perturbations
- Reachability (explicit)

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Analysis methods

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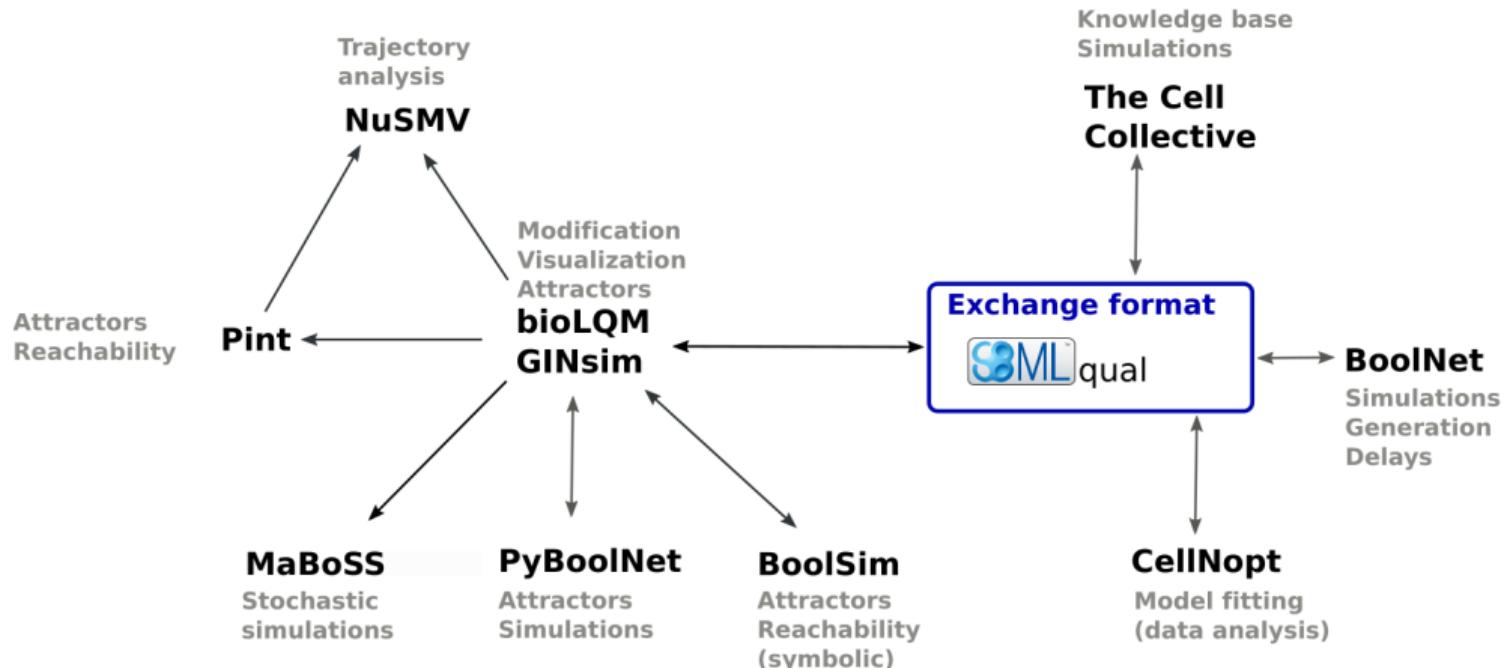
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Other tools exist, though!

		Trajectory analysis	Knowledge base Simulations
		NuSMV	The Cell Collective
Attractors Reachability	Pint	Modification Visualization Attractors bioLQM GINsim	BoolNet Simulations Generation Delays
MaBoSS Stochastic simulations	PyBoolNet	BoolSim Attractors Reachability (symbolic)	CellNopt Model fitting (data analysis)



Full list of available tools: <https://colomoto.github.io/colomoto-docker/>

Consortium for Logical Models and Tools



Install

Conda packages, Docker image



Perform analysis

Python API for all tools

Jupyter: semi-interactive interface



Share

Analysis: Jupyter notebooks

Models: SBML qual exchange format



Try it online (No installation)

Limited resources, download to save

tmpnb.colomoto.org



colomoto-docker (requires docker and Python)

Python wrapper hiding complex docker commands

Pure Docker

Raw Docker commands

Conda packages

Linux only, less reproducible

(Naldi *et al.*, *Frontiers in Physiology* 2018)

Maintained (mainly) by:



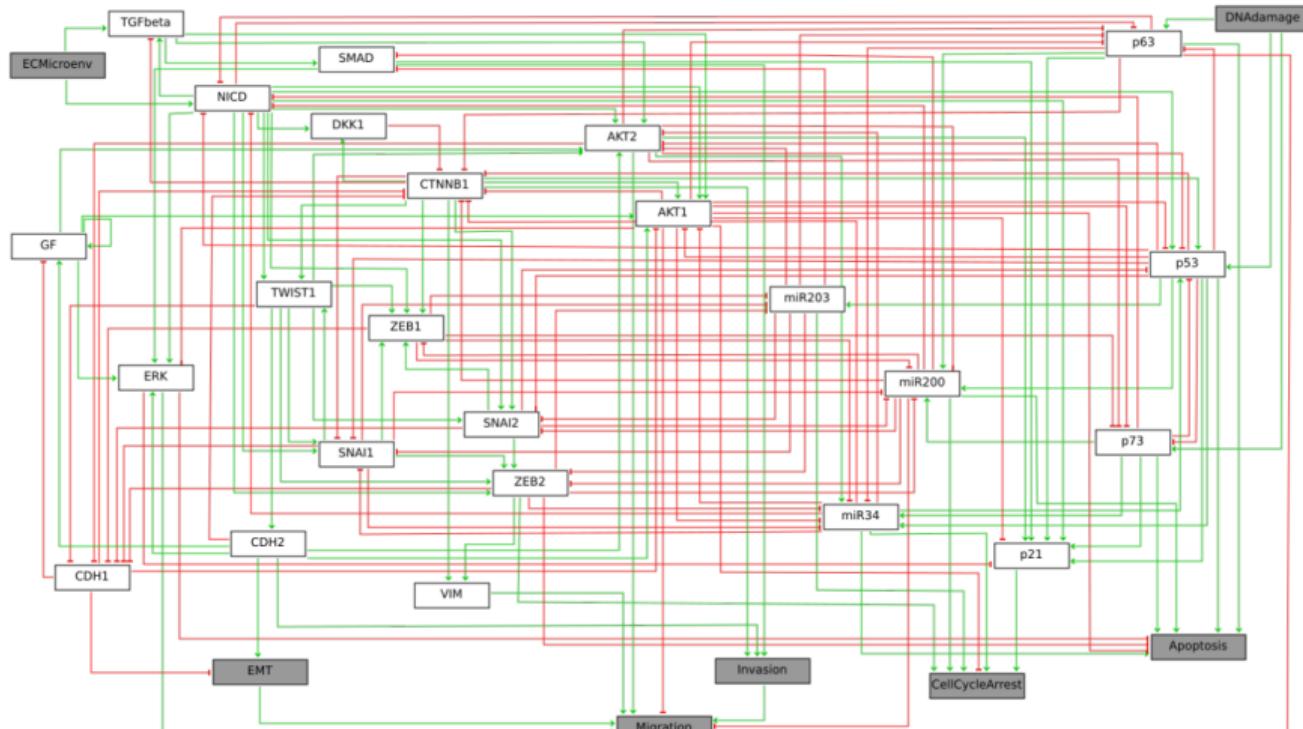
Aurélien Naldi



Loic Paulevé

Load and view models

```
1 lrg = ginsim.load("Cell_Fate_Master_Model.zginml")
2 ginsim.show(lrg)
```



Models modifications

Perturbations

bioLQM

```
1 mlqm = biolqm.perturbation(lqm, "TGFb%0")
```

```
1 biolqm.perturbation(lqm, "TGFb:AKT2%0")
```

```
1 biolqm.perturbation(lqm, "TGFb%1:2")
```

Pint

```
1 an.lock(TGFb=0)
```

Remove an interaction

MaBoSS

```
1 masim.mutate("TGFb", "OFF")
```

Range Restriction (multivalued)

Multivalued to Boolean

```
1 blqm = biolqm.booleanize(lqm)
```

Model reduction

```
1 reduced = biolqm.reduce(lqm, "fixed,outputs")
```

Identification of attractors

```

1 lqm = ginsim.to_biolqm(lrg)
2 fixpoints = biolqm.fixpoints(lqm)
3 tabulate(fixpoints)

```

```

1 an = ginsim.to_pint(lrg)
2 fixpoints = an.fixpoints()
3 tabulate(fixpoints)

```

ECMicroenv	DNAAdamage	Metastasis	Migration	Invasion	EMT	Apoptosis	CellCycleArrest	GF	TGFbeta	p21	CDH1	CDH2	VIM	TWIST1	SNAI1
0	0	0	0	0	0	0		0	0	0	1	0	0	0	0
1	0	0	0	0	0	1	0	1	1	0	0	0	1	1	1
2	0	1	0	0	0	0	1	1	0	0	1	1	0	0	0
3	0	1	0	0	0	0	1	1	0	0	1	1	0	0	0
4	0	1	0	0	0	1	0	1	1	0	0	0	1	1	1
5	1	0	1	1	1	1	0	1	1	1	0	0	1	1	1
6	1	1	0	0	0	0	1	1	0	1	1	1	0	0	0

```

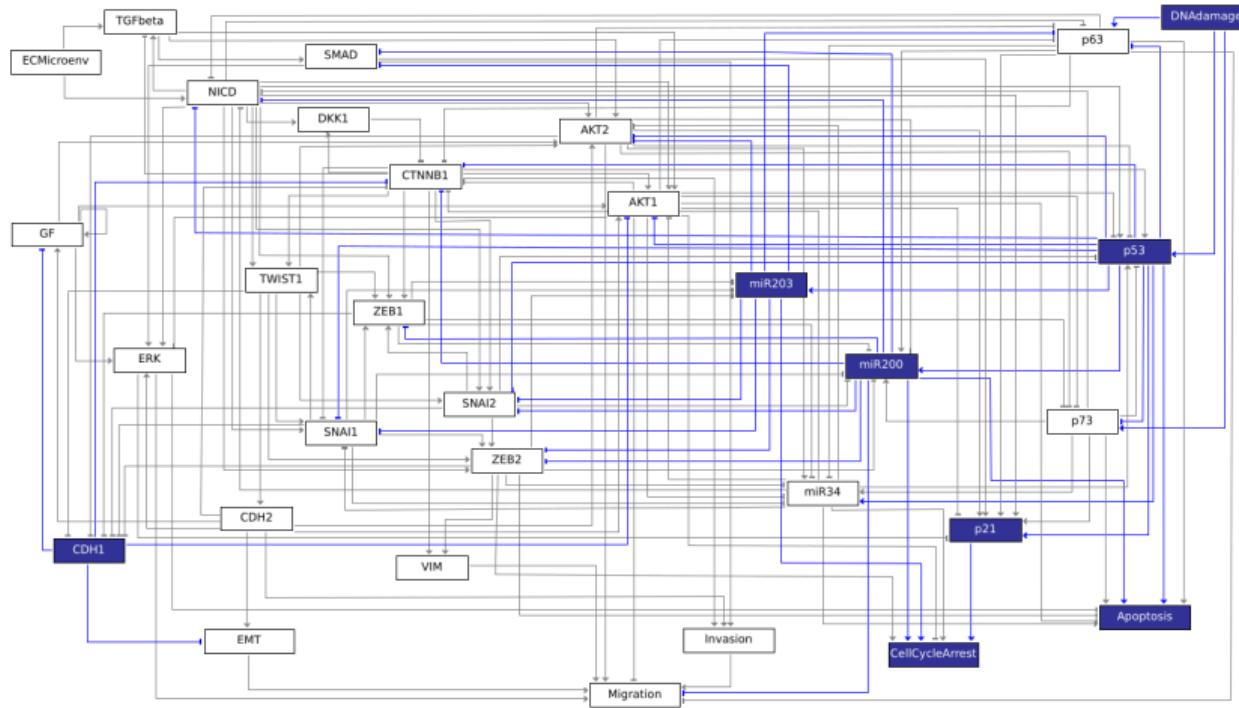
1 trapspaces = biolqm.trapspaces(lqm)
2 tabulate(trapspaces)

```

CycD	Rb	E2F	CycE	CycA	p27	Cdc20	cdh1	UbcH10	CycB	
0	0	1	0	0	0	1	0	1	0	0
1	1	0	254	254	254	0	254	254	254	254

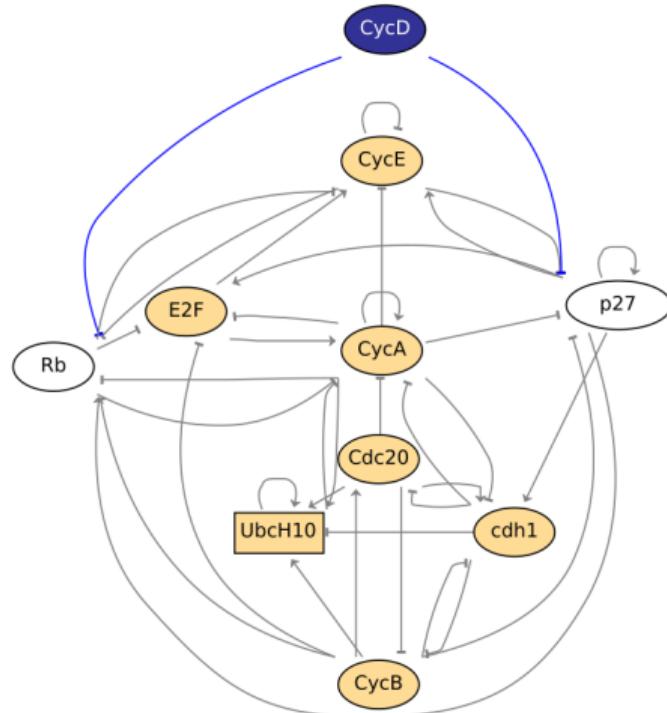
Map results on the model view

```
1 ginsim.show(lrg, fixpoints[2])
```



Map results on the model view

```
1 ginsim.show(lrg, trapspaces[1])
```



Formal reachability analysis

Pint

```
1 an = biolqm.to_pint(lqm)
2 target_state = {"Apoptosis":1}
3 an.reachability(goal=target_state)
```

True

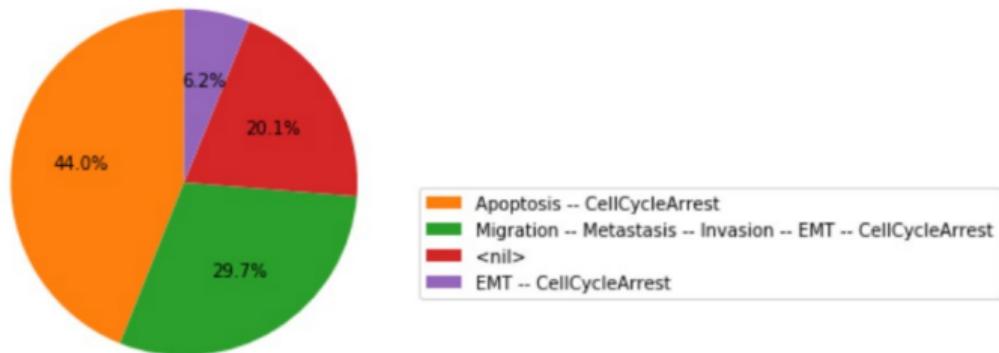
NuSMV model checker

```
1 smv = an.to_nusmv()
2 ctl_specs = {
3     "stable-apoptosis": EF(AG(S(Apoptosis=1)))
4 }
5 smv.add_ctls(ctl_specs)
6 smv.verify()

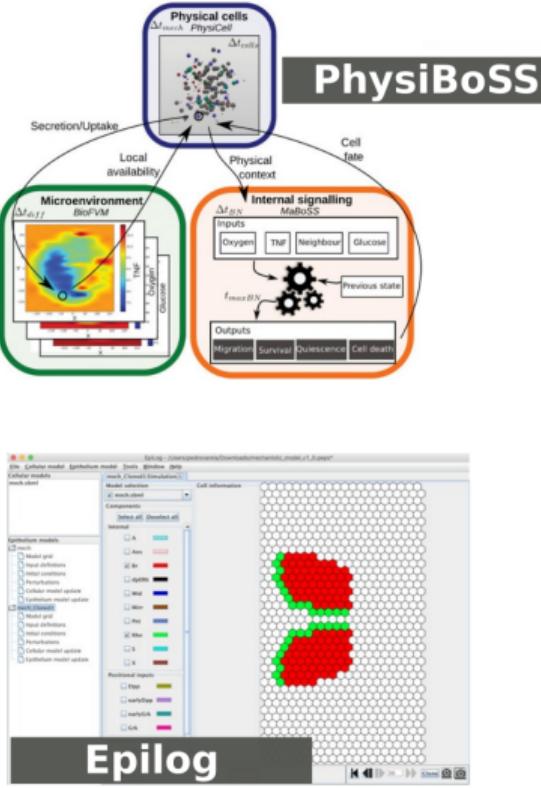
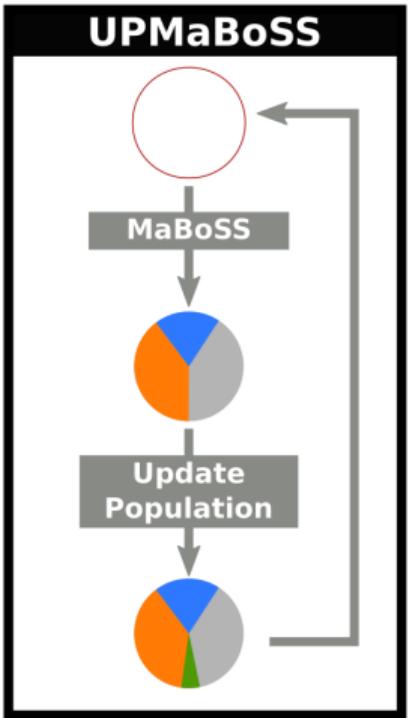
{'stable-apoptosis': False}
```

Estimation of reachability probabilities

```
1 masim = biolqm.to_maboss(lqm)
2 mares = masim.run()
3 mares.plot_piechart()
```



Multicellular logical modeling...



EpiLog (Varela et al., *F1000Research* 2019)

Break....



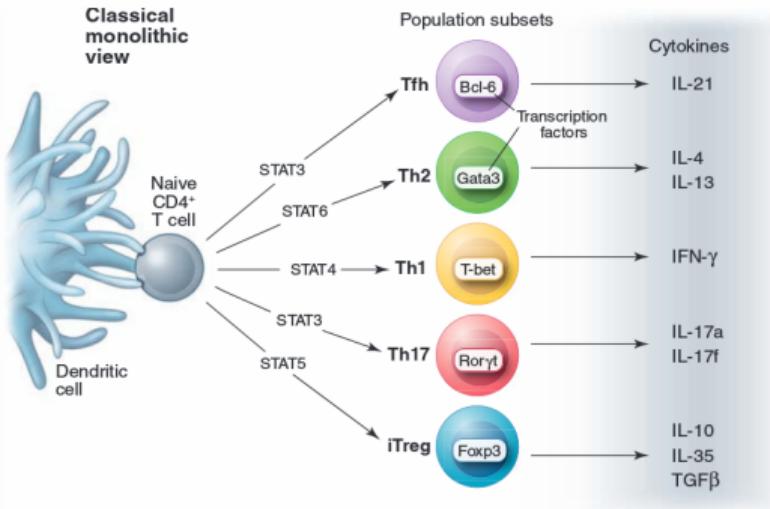
Mechanisms Underlying Lineage Commitment and Plasticity of Helper CD4⁺ T Cells

John J. O'Shea* and William E. Paul

CD4⁺ T cells are critical for host defense but are also major drivers of immune-mediated disease. These T cells specialize to become distinct subsets and produce restricted patterns of cytokines, which are tailored to combat various microbial pathogens. Although classically viewed as distinct lineages, recent work calls into question whether helper CD4⁺ T cell subsets are more appropriately viewed as terminally differentiated cells or works in progress. Herein, we review recent advances that pertain to this topic and the mechanisms that contribute to helper CD4⁺ T cell commitment and plasticity. The therapeutic implications of these new findings are also considered.

(O'Shea and Paul, *Science* 2010)

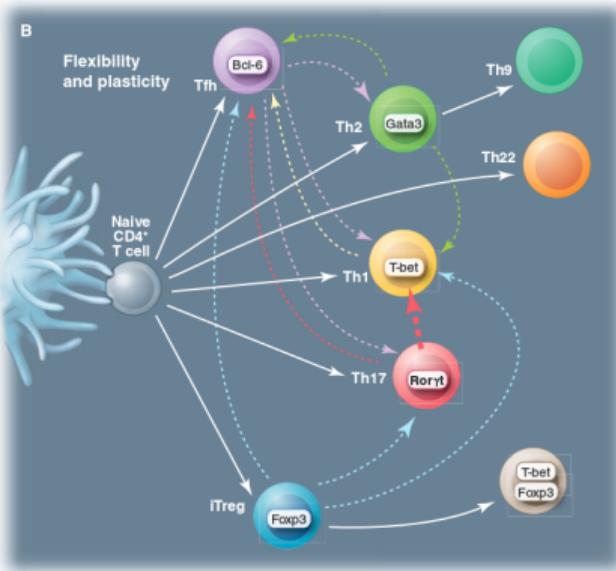
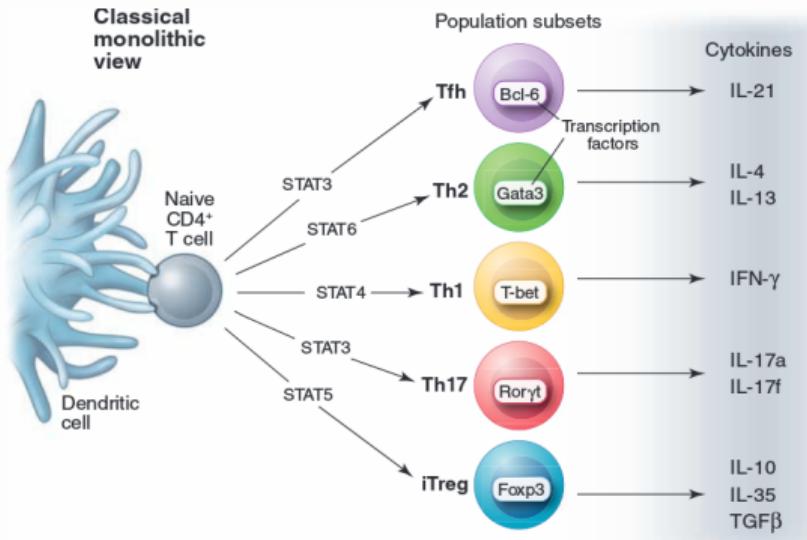
Case study - T-helper cell differentiation



- T-helper (CD4+) lymphocytes play a role in the regulation of immune responses
- Faced with pathogens, naive CD4+ T cells differentiate into distinct Th cell populations expressing distinct cytokine profiles
- Polarization into cell types is governed by transcription factors

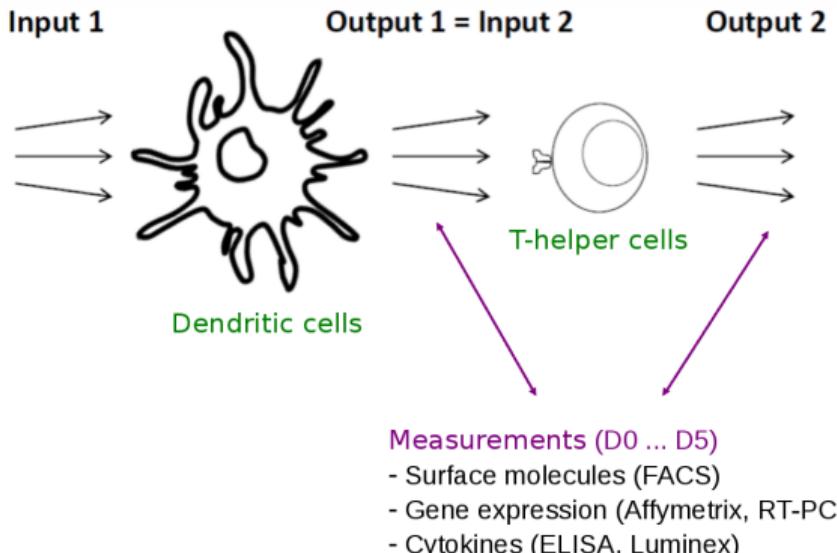
(O'Shea and Paul, *Science* 2010)

Case study - T-helper cell differentiation



Objective

- Model capable of reproducing Th cell differentiation
Extension of ([Naldi et al., PLoS Comput. Biol. 2010](#))
- Capable of exhibiting plasticity behaviours

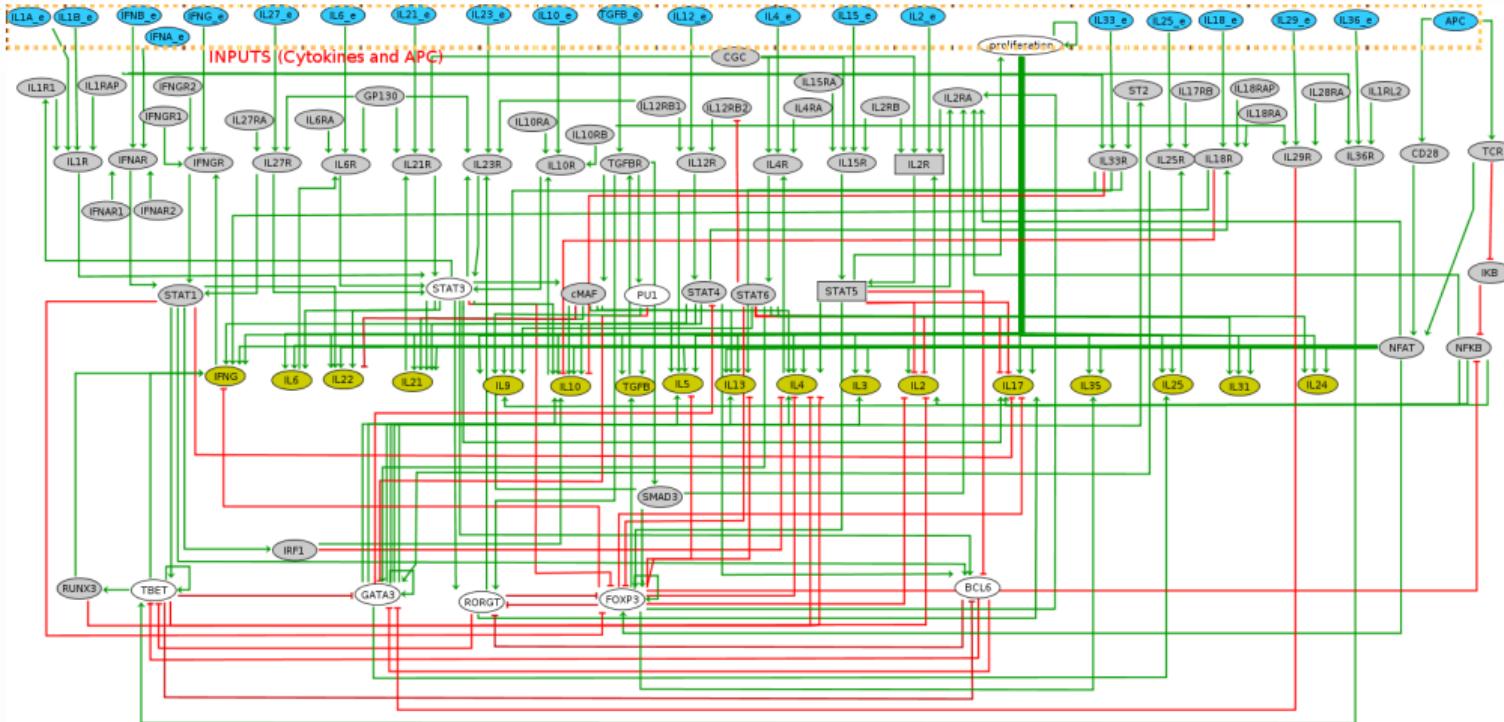


Maximilien Grandclaudon
Vassili Soumelis



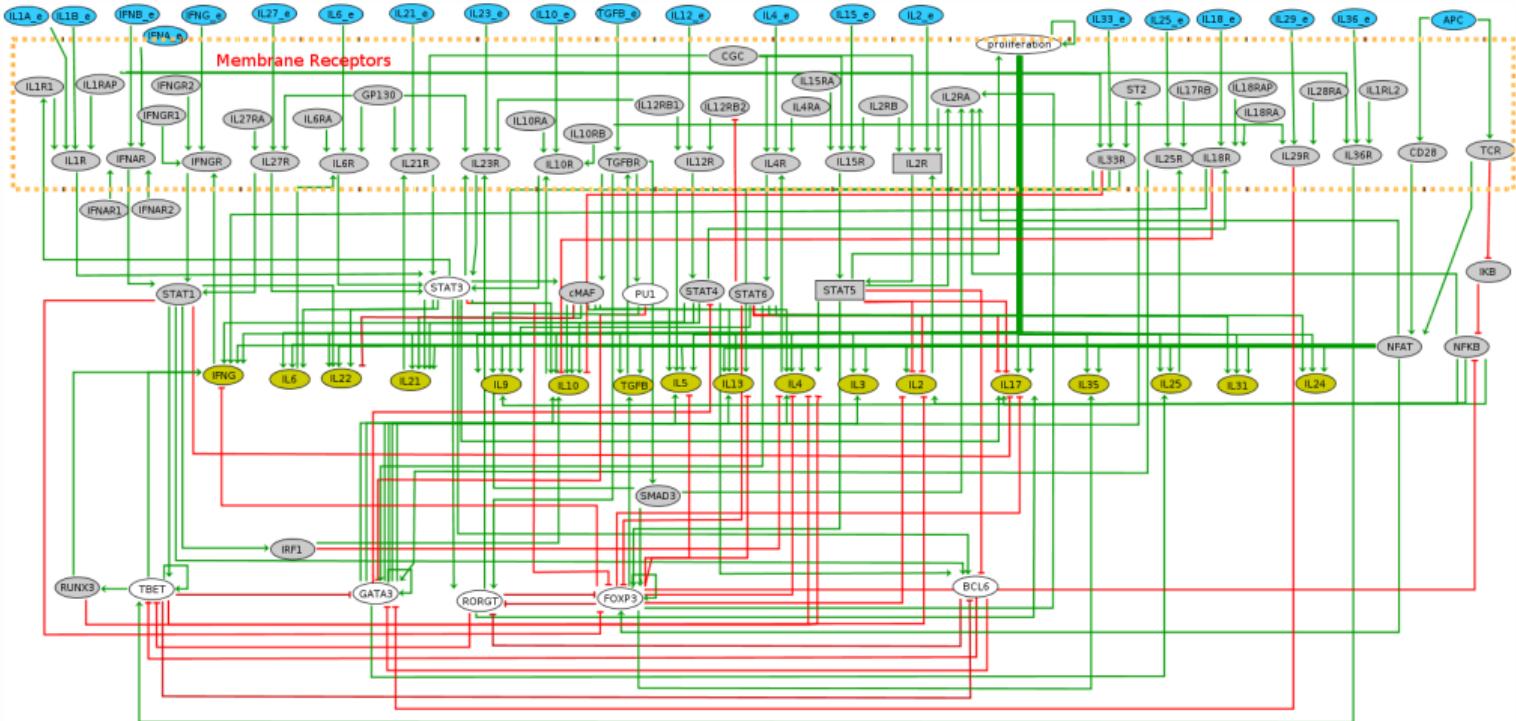
Wassim Abou-Jaoudé
Denis Thieffry

Logical modelling of the Th network



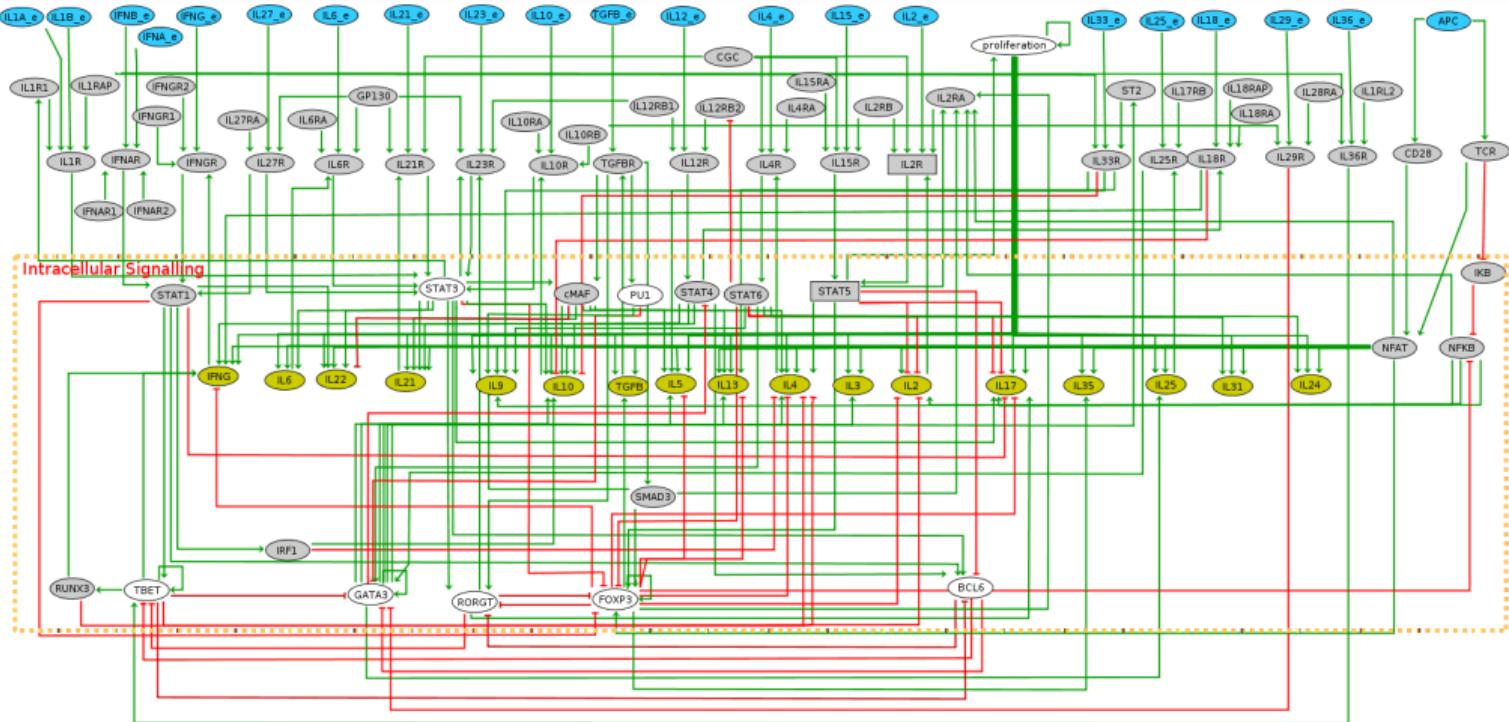
(Abou-Jaoudé et al, *Frontiers in Bioeng. Biotech.* 2015)

Logical modelling of the Th network



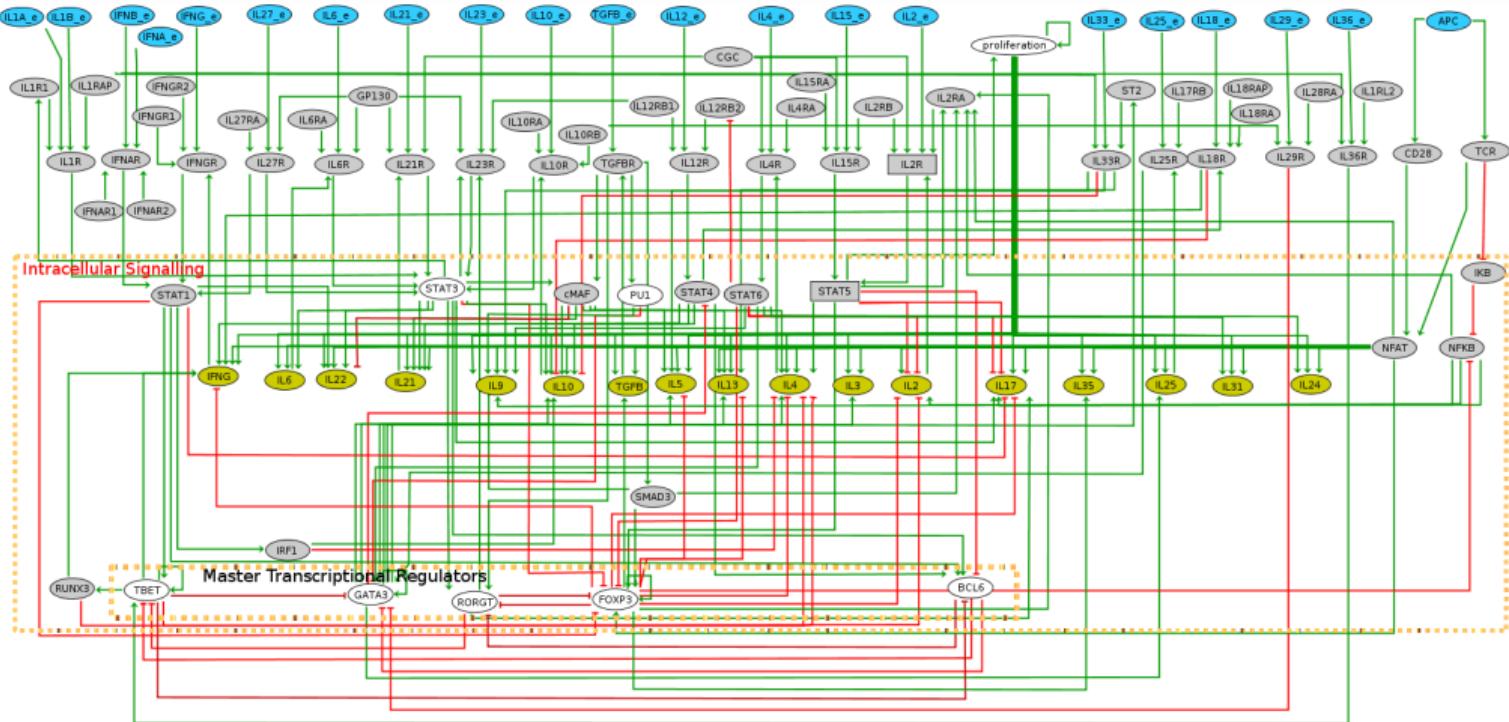
(Abou-Jaoudé et al, *Frontiers in Bioeng. Biotech.* 2015)

Logical modelling of the Th network



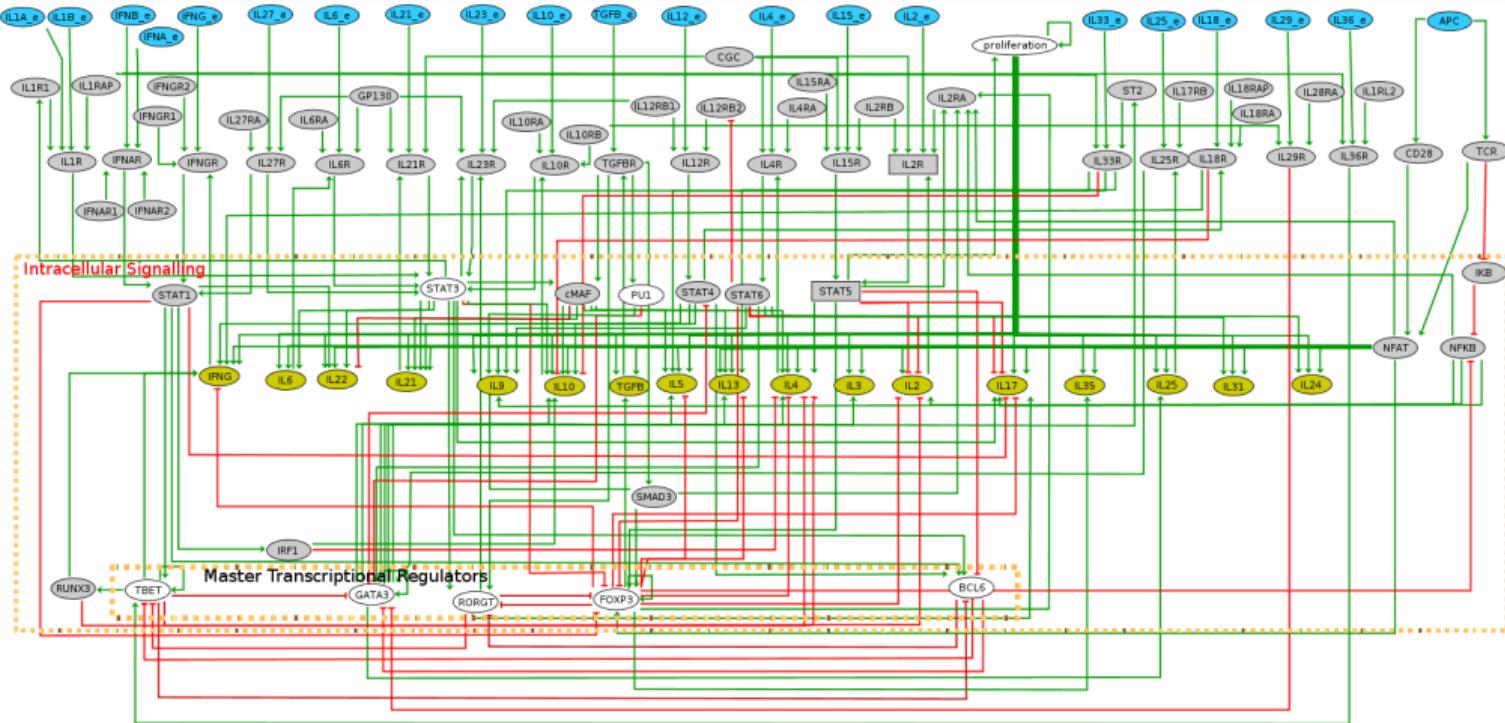
(Abou-Jaoudé et al, *Frontiers in Bioeng. Biotech.* 2015)

Logical modelling of the Th network



(Abou-Jaoudé et al, Frontiers in Bioeng. Biotech. 2015)

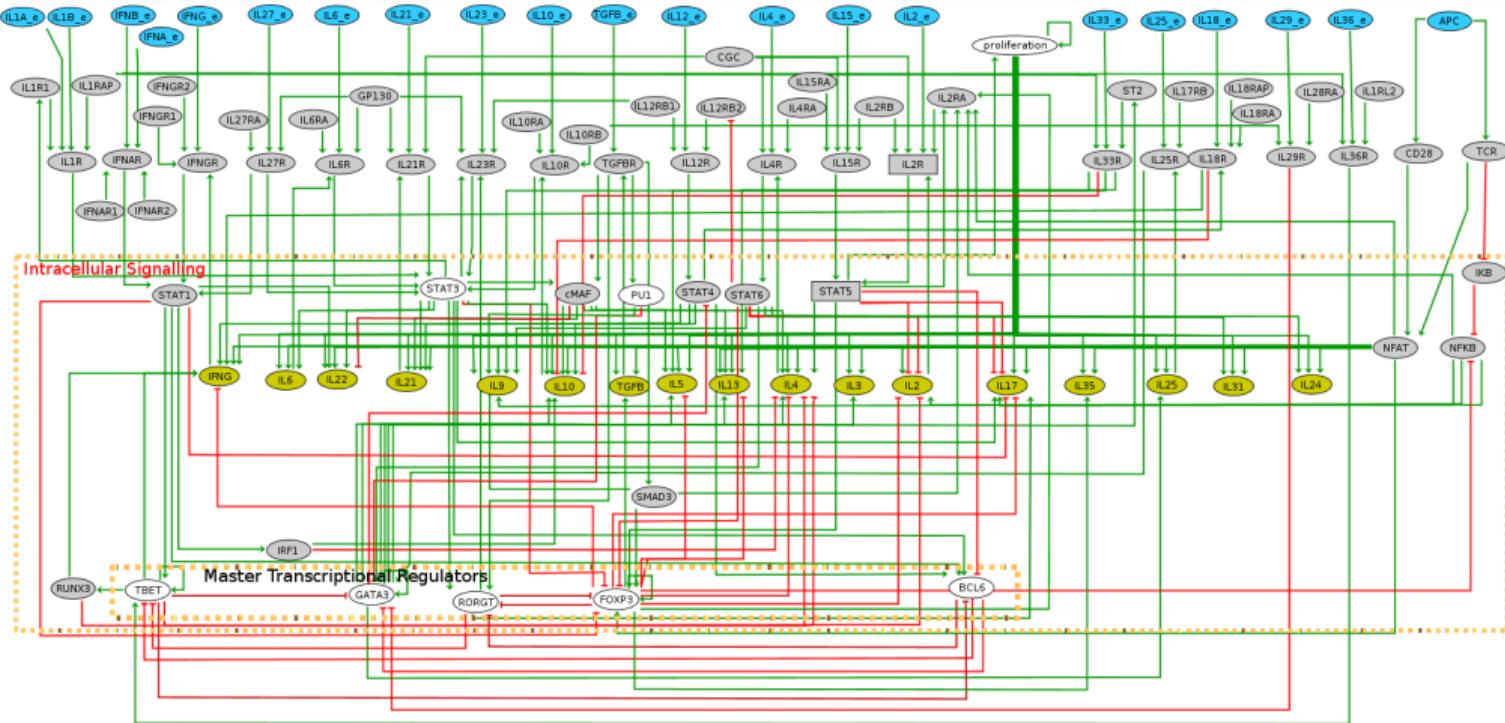
Logical modelling of the Th network



(Abou-Jaoudé et al, *Frontiers in Bioeng. Biotech.* 2015)

Model size: 101 components (21 inputs + 80 internal) and 221 interactions

Logical modelling of the Th network



(Abou-Jaoudé et al, *Frontiers in Bioeng. Biotech.* 2015)

Model size: 101 components (21 inputs + 80 internal) and 221 interactions

STG size: $2^{21} \times 3^2 \times 2^{78} = 5704427701027032306735164424192$ states!!

Pedro → Mota To notebook @ WTAC

Approach to analyse the T-helper cell differentiation model:

- Identify the biologically relevant **states** corresponding to **Th cell subtypes**
- Automatically compute the **reprogramming and plasticity** between **Th cell subtypes**

Start by computing the set of biologically relevant **Th** cell subtypes

	Transcription factors						Secreted cytokines									
	TBET	GATA3	RORGT	FOXP3	BCL6	PU.1	STAT3	IFNG	IL4	IL17	IL21	IL22	IL5	IL13	IL9	TGFB
Th0																
Th1	Red							Red								
Th2	Green	Red						Green	Red	Green			Red			
Th17		Red	Red					Green	Red	Red						
Treg			Red					Green						Red		
Tfh				Red				Green		Red						
Th9					Red			Green					Red			
Th22						Red		Green			Red					

(Abou-Jaoudé et al., *Frontiers in Bioeng. Biotech.* 2015)

Then characterize the set of prototypic **environmental conditions**

	Environmental conditions								
	APC	IL12_e	IL4_e	IL6_e	TGF β _e	IL1B_e	IL23_e	IL21_e	IL2_e
no stimulation									
APC only	Red								
proTh1		Red							
proTh2			Red						
proTh17				Red	Red	Red			
proTreg					Red				
proTfh						Red	Red		
proTh9					Red				
proTh22									

(Abou-Jaoudé *et al.*, *Frontiers in Bioeng. Biotech.* 2015)

Then characterize the set of prototypic **environmental conditions**

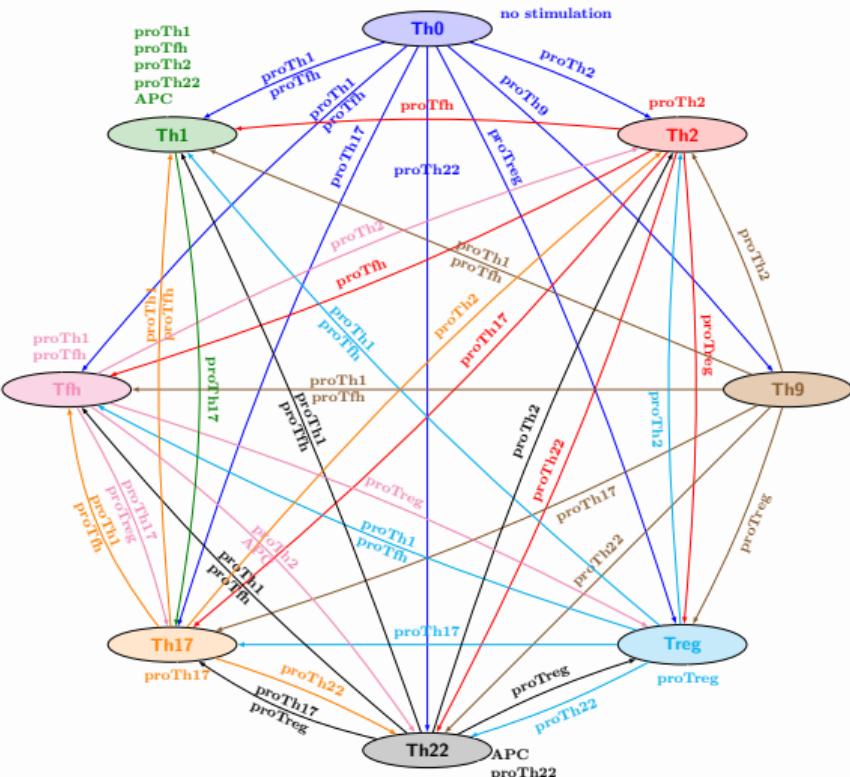
	Environmental conditions								
	APC	IL12_e	IL4_e	IL6_e	TGF β _e	IL1B_e	IL23_e	IL21_e	IL2_e
no stimulation									
APC only	Red								
proTh1		Red							
proTh2			Red						
proTh17				Red	Red	Red			
proTreg					Red				
proTfh							Red	Red	
proTh9					Red				
proTh22									

(Abou-Jaoudé et al., *Frontiers in Bioeng. Biotech.* 2015)

Still have a reachability problem on a **very** large STG! ($\approx 2^{100}$ states)

Case study - Reachability analysis of relevant Th cell subtypes

Use model checking to systematically explore the reachability of all **Th cell subtypes** under all **environmental/input conditions**



Model repository

http://ginsim.org/models_repository



The screenshot shows the GINsim Model Repository homepage. At the top, there is a navigation bar with links: HOME, DOCUMENTATION, MODEL REPOSITORY (which is highlighted in red), DOWNLOADS, PUBLICATIONS, COMPANION TOOLS, and CONTACTS & TERMS. Below the navigation bar, there is a search bar with a placeholder "Search" and a "Search" button. To the left of the search bar is a logo for "GINsim" with a small diagram of a cell. The main content area is titled "Browse Models". It features a table with columns for "Title", "Taxon", and "Process". The table lists various models, their taxonomic information, and biological processes they are associated with.

Browse Models

Title	Taxon	Process
Asymmetric Cell Division in Caulobacter Crescentus	Bacterium, C. Crescentus	Cell cycle, Asymmetric cell division
Boolean model of geroconversion	Mammal	Senescence
Budding yeast cell cycle (adapted from Irons, 2009)	Budding yeast, Yeast	Cell cycle
Budding yeast cell cycle (Fauré et al. 2009)	Budding yeast, Yeast	Cell cycle
Budding yeast cell cycle (Orlando et al. 2008)	Budding yeast, Yeast	Cell cycle
Budding yeast exit module	Budding yeast, Yeast	Cell cycle, Mitosis exit control
Cell fate decision network in the AGS gastric cancer cell line (Flobak et al 2015)	Mammal	Cancer
Cell-Fate Decision in Response to Death Receptor Engagement	Mammal	Cell fate decision
Contribution of ROS and metabolic status to neonatal and adult CD8+ T cell activation	Mammal, Human	T-cell activation
Control of proliferation by oncogenes and tumor suppressors	Mammal	Cell fate decision
Control of Th1/Th2 cell differentiation	Mammal	Differentiation
OmniOpTh1/Th2/Th17/Treg cells differentiation	Mammal	Differentiation

- Load the Th model from GINsim model repository
<http://ginsim.org/sites/default/files/Frontiers-Th-Full-model-annotated.zginml>
but for practical reasons (time/memory) we'll use the older/simpler model
http://ginsim.org/sites/default/files/Th_17.zginml (Mendoza 2006)
http://ginsim.org/sites/default/files/Th_differentiation_reduced_model.zginml (Naldi 2010)
- Display the regulatory graph
- Compute all stable states using the `biolqm` (and then `pint`) python modules
- Visualise the n^{th} stable state
- Perform reachability analysis using `boolsim`, `NuSMV`, ...

Hint: note the menus (command shortcuts) on top of notebook